(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 September 2004 (02.09.2004)

PCT

(10) International Publication Number
WO 2004/073689 A1

(51) International Patent Classification[7]: A61K 9/18, 9/20

(21) International Application Number:
PCT/DK2004/000112

(22) International Filing Date: 18 February 2004 (18.02.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

PA 2003 00252	19 February 2003 (19.02.2003)	DK
PA 2003 01013	3 July 2003 (03.07.2003)	DK

(71) Applicant *(for all designated States except US)*: **LIFECYCLE PHARMA A/S** [DK/DK]; Kogle Alle 4, DK-2970 Hørsholm (DK).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HOLM, Per** [DK/DK]; Grøndals Parkvej 54, DK-2720 Vanløse (DK). **NORLING, Tomas** [DK/DK]; Møllevænget 36, DK-2800 Lyngby (DK). **ELIASEN, Helle** [DK/DK]; Munkekærgård 9, DK-4600 Køge (DK).

(74) Agent: **ALBIHNS A/S**; H.C. Andersens Boulevard 49, DK-1553 Copenhagen V (DK).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF A SILICA OR SILICA DERIVATIVE AS A SORPTION MATERIAL

(57) Abstract: Use of a silica or silica derivative such as, e.g., Aeroperl® as a sorption material for oils or oily-like materials. The silica or silica derivates has the ability to be loaded with a relative high amount of the oil or oily-like material and this ability is especially useful concerning formulation of pharmaceutical compositions comprising a drug substance suffering from e.g. bioavailability and/or water-solubility problems. Furthermore, the silica or silica derivative has the ability to release the oil or oily-like material when contacted with an aqueous medium and/or it has suitable tabletting properties.

WO 2004/073689 A1

USE OF A SILICA OR SILICA DERIVATIVE AS A SORPTION MATERIAL

Field of the invention

The present invention relates to the use of silica or silica derivative in solid form as a sorption material for liquid material or material that has a melting point below about 250 °C; in the following denoted oils and/or oily-like materials. The use of the silica or silica derivative is suitable in formulation of pharmaceutical, cosmetic and/or foodstuff compositions, especially in those situations where the compositions are presented in solid form although they contain a relatively large amount of oil or an oily-like material.

In another aspect, the invention relates to a solid pharmaceutical particulate material or a solid pharmaceutical composition comprising

i) an oil or an oily-like material,

ii) a sorption material for oils or oily-like materials as defined herein,

wherein the concentration of the oil or oily-like material in the particulate material is about 5% w/w or more.

Background of the invention

Many drug substances have and it is expected that many of the future drug substances will have undesired properties especially with respect to water solubility and to oral bioavailability. Therefore, novel technologies, which enable especially therapeutically and/or prophylactically active substances to be delivered to the body in a relatively easy manner and at the same time enables the desired therapeutic and/or prophylactic response, is highly needed.

In the pharmaceutical area it is common to prepare pharmaceutical compositions comprising one or more active compounds and various excipients. One reason for preparing such pharmaceutical compositions is to manipulate the availability of the active compound after ingestion of the pharmaceutical composition.

For the preparation of pharmaceutical composition for oral administering the active compounds are often incorporated into an agglomerated preparation in order to provide the active compounds in a form that may be pressed into tablets or filled into capsules.

Beside providing the active compound in a form that may be pressed into tablets, agglomerates may also be designed to secure a desired availability of the active compound after ingestion of a pharmaceutical composition containing said granule.

One commonly used technique for granulation is a wet granulation, where a mixture of powders including the active compound is mixed with a liquid, usually an aqueous liquid, under mechanical influence for the preparation of granules. Usually the granules prepared by wet granulation are dried before use.

Melt agglomeration and controlled agglomeration are techniques for agglomeration of an active compound, essentially performed by melting a pharmaceutical acceptable vehicle such as an oil or an oily-like material, dissolution or dispersion of one or more active compounds in the melted vehicle and deposition of the thus prepared mixture on a particulate material, the filler, and subsequently the particles adhere to each other and form agglomerates.

In WO 03/004001 (by the present inventors) is described the novel technique of controlled agglomeration by which it is possible to load a particulate material with a relatively high amount of an oil or an oily-like material. The technique is based on a process that involves spraying of a carrier composition containing the oil or oily-like material onto a particulate material. The process conditions enable the particulate material to be loaded with a relatively high amount of the oil or oily-like material. Normally, the process involves heating of the carrier composition and maintaining the temperature of the carrier composition during application. As the application is performed by spraying, strict temperature control of the spraying equipment is a requirement in order to avoid problems relating to clotting of the spray nozzle etc.

The present inventors have now found a more simple solution. They have found that some silica or silica derivatives have the ability to absorb or adsorb oils or oily-like materials. To the best of the inventors knowledge, this ability has not been recognized or used before in the pharmaceutical field and the present inventors have found that this ability can be utilized in the preparation of compositions having a relatively high content of an oil or an oily-like material and, especially, it is suitable for use in the controlled agglomeration process involving relatively insoluble drug substances.

Description of the invention

The enhancement of oral bioavailability of poorly water soluble drugs as well as providing a fairly water soluble drug in a sustained release form remain one of the most challenging aspects of drug development and further development of the agglomeration techniques

may provide valuable tools for these aspects.

The present inventors have surprisingly found that specific types of silica or silica derivatives have suitable properties with respect to uptake of liquids or melted materials, i.e. materials that have a melting point above ambient temperature. This feature can be used in the development of pharmaceutical formulation such as e.g. within formulations based on agglomeration techniques.

Thus the present invention relates to new and useful agglomerated pharmaceutical compositions comprising a silica or silica derivative and a pharmaceutically, prophylactically and/or diagnostically active compound.

It has surprisingly been found that the compositions (such as e.g. agglomerated compositions) according to the invention can contain a high amount of an oil or oily-like material having active compounds dissolved or dispersed therein.

This surprising realization provides the advantage that pharmaceutical compositions for oral ingestion such as tablets or capsules prepared using the agglomerated compositions according to the invention having a higher content of vehicle and/or the active compound can be manufactured. Alternatively smaller tablets may be prepared with the following improved acceptance by the consumer and a reduced consumption of excipients, tablet additives, coatings etc. for the manufacturer. Further, a higher amount of oil or oily-like material may be incorporated into a pharmaceutical composition in order to improve the bioavailability of the active compound.

Further the agglomerated compositions according to the invention can easily be compressed into tablets.

In another aspect the invention relates to a procedure for the preparation of the agglomerated composition.

In the present specification the term "controlled agglomeration" is used for a process for preparing a material where a melt of an oil or an oily-like material optionally comprising an active substance is deposited on a solid composition to enable the formation of an agglomerate. The term is also defined in WO 03/004001 to which reference is made, and which is hereby incorporated by reference in its entirety.

The term "agglomerate" is used in the usual meaning i.e. a material composed of agglomerated primary particles. It is usually preferred to prepare agglomerates comprising active compounds before these are manufactured into pharmaceutical composition. Agglomerates provide the benefits of less dusting during handling thereof compared with powders, as well as excellent flowability.

As used herein, "particle volume size distribution" means the distribution of equivalent spherical diameters as determined by laser diffraction at 0.2 bar dispersive pressure in a Sympatec Helos equipment. "Median particle size", correspondingly, means the median of said particle size distribution.

Silica such as silicon dioxide is a well-known compound for pharmaceutical use having a number of known uses. The pharmaceutical use of silicon dioxide has been described in the well recognized "Handbook of Pharmaceutical Excipients, 3rd ed. 2000, Published by the American Pharmaceutical Association, 2215 Constitution Avenue, NW Washington, DC 20037-2985 USA and the Pharmaceutical Press, 1 Lamberth High Street, London, UK; as adsorbent, anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent. Despite of the wide use of silicon dioxide within the pharmaceutical area the use as filler in a melt agglomeration process is new.

It is surprising that a melt agglomerate having silicon dioxide as filler may be used for the manufacture of pharmaceutical compositions because one would expect that the active compound comprised in said agglomerate would not be released at a sufficiently high rate because the silicon dioxide does not dissolve in the gastrointestinal tract and it may even provide a viscous gel.

The present invention relates to the use of a silica or silica derivative, which - when tested as described herein -

i) has an oil threshold value of 10% or more, when tested according to the Threshold Test herein,

ii) has a bulk density of at least about 15 g/100 ml,

and at least one of

iii) releases at least 30% of an oil, when tested according to the Release Test herein, and

iv) in the form of a tablet has a disintegration time of at the most 1 hour, when tested according to Ph. Eur. Disintegration test, the tablet containing about 90% w/w or more of the silica or silica derivative,

v) in the form of a tablet has a tablet hardness of at least about 10 N when tested as described herein,

as a sorption material for oils or oily-like materials.

The material is especially useful as a sorption material for oils or oily-like materials in pharmaceuticals, cosmetics and/or foodstuff. In a specific embodiment, the material is for use as a sorption material for oils or oily-like materials in pharmaceuticals.

In the following the silica or silica derivative that has the ability to function as a sorption material for oils or oily-like materials is also denoted "oil sorption material". Furthermore, in the present context the term "sorption" is used to denote "absorption" as well as "adsorption". It should be understood that whenever one of the terms is used it is intended to cover the phenomenon absorption as well as adsorption.

As it appears from the above, it is important that the oil sorption material fulfils at least three tests. Two of the tests are mandatory, i.e. the Threshold Test and the requirements with respect to bulk density must be met. The Threshold Test gives a measure for how much oil or oily-like material the oil sorption material is able to absorb while retaining suitable flowability properties. It is important that an oil sorption material according to the invention (with or without oil absorbed) has a suitable flowability so that it easily can be admixed with other excipients and/or further processed into compositions without significant problems relating to e.g. adherence to the apparatus involved. The test is described in the Experimental section herein and guidance is given for how the test is carried out. The Threshold Test involves the determination of the flowability of the solid material loaded with different amounts of oil.

From above it is seen that the oil threshold value normally must exceed 10% and often the oil sorption material has an oil threshold value of at least about 15%, such as, e.g., at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, or at least about 45%.

An especially suitable material for use according to the invention, Aeroperl® such as, e.g., Aeroperl® 300, has a very high oil threshold value of about 60%. Accordingly, materials that have an oil threshold value of at least about 50%, such as, e.g., at least about 55% or at least about 60% are specific embodiments of the present invention.

The other mandatory requirement is with respect to bulk density. The silica or silica derivative used as an oil sorption material must have a bulk density that is at least about 15 g/100 ml such as, e.g., from about 15 to about 30 g/100 ml, from about 17 to about 28 g/100ml, from about 19 to about 25 g/100 ml, from about 20 to about 25 g/100 ml, from about 20 to about 23 g/ml such as about 21 g/100 ml.

In another embodiment the silica or silica derivative has a tapped density of at least about 20 g/100 ml such as, e.g., at least about 22 g/100 ml, at least about 25 g/100 ml, at least about 26 g/100 ml, at least about 27 g/100 ml, and/or at the most about 40 g/100 ml such as, e.g. at the most about 35 g/100 ml or at the most about 30 g/100 ml.

Furthermore, an oil sorption material according to the invention must fulfill at least one further test, namely a release test, a disintegration test and a tablet hardness test.

The release test gives a measure of the ability of an oil sorption material to release the oil that is absorbed to the material when contacted with water. This ability is very important especially in those situations where an active substance is contained in the oil or oily-like material. If the oil sorption material is not capable of releasing the oil from the material then there is a major risk that the active substance will only to a minor degree be released from the material. Accordingly, it is envisaged that bioavailability problems relating to e.g. poor absorption etc. will occur in such situations.

The requirements for the release test are that the solid pharmaceutical acceptable material - when tested as described herein -

ii) releases at least about 30% such as, e.g., at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 60% of an oil.

As it appears from the examples herein a suitable oil sorption material like Aeroperl® such as, e.g., Aeroperl® 300, has a much higher release. Therefore, in a specific embodiment of the invention, the solid pharmaceutical acceptable material - when tested as described herein -

ii) releases at least about 65% such as, e.g., at least about 70%, at least about 75% or at least about 80% of an oil.

The second of the tests at least one of which an oil sorption material according to the invention must fulfil is a disintegration test. The test is not performed on the solid material in particular form but on a tablet made of the solid material. A requirement with respect to disintegration is important in order to ensure that the solid material – when included in

solid dosage forms – does not impart unwanted properties to the dosage form e.g. leading to unwanted properties with respect to dissolution and bioavailability of the active substance contained in the dosage form. For some of the materials suitable for use according to the invention it is possible to press tablets containing 100% w/w of the solid material itself. If this is the case, the test is carried out on such tablets. However, it is envisaged that there may be situations where it is rather difficult to prepare tablets from the solid material alone. In such cases it is possible to add pharmaceutically acceptable excipients normally used in the preparation of compressed tablets up to a concentration of 10% w/w or less. Examples on suitable pharmaceutically acceptable excipients include fillers, diluents, binders and lubricants. However, excipients, normally classified as disintegrants, should be avoided. However, it should be noted that it is preferred to avoid any addition of pharmaceutically acceptable excipients when carrying out this test. With respect to Aeroperl® it has been shown that it is not necessary to add any pharmaceutically acceptable excipients in order to enable tabletting of Aeroperl® itself.

Accordingly, the solid pharmaceutical acceptable material for use according to invention- when tested as described herein

iii) in the form of a tablet should have a disintegration time of at the most 1 hour, when tested according to Ph. Eur. Disintegration test, the tablet containing about 90% w/w or more, such as, e.g., about 92.5% w/w or more, about 95% w/w or more, about 97.5% w/w or more or about 100% of the pharmaceutically acceptable material.

In a further embodiment, the solid pharmaceutical acceptable material - when tested as described herein

iii) in the form of a tablet has a disintegration time of at the most about 50 min, such as, e.g., at the most about 40 min, at the most about 30 min, at the most about 20 min, at the most about 10 min or at the most about 5 min, when tested according to Ph. Eur. Disintegration test, the tablet containing about 90% w/w or more, such as, e.g., about 92.5% w/w or more, about 95% w/w or more, about 97.5% w/w or more or about 100% of the pharmaceutically acceptable material.

The third of the tests at least one of which an oil sorption material according to the invention must fulfil is a tablet hardness test. In accordance with the disintegration test mentioned above. The test is not performed on the solid material in particular form but on a tablet made of the solid material. In order to ensure that the properties of the silica or silica derivative are suitable for manufacturing of pharmaceutical composition and especially for manufacturing of tablets, it is desirable that the silica or silica derivative

does not impart poor tablet hardness to such tablets. According a certain tablet hardness is desirable (but not to such an extent that the disintegration time is impaired). Accordingly, the silica or silica derivative in the form of a tablet containing about 90% w/w or more, such as, e.g., about 92.5% w/w or more, about 95% w/w or more, about 97.5% w/w or more or about 100% of the silica or silica derivative has a tablet hardness of at least about 10 N such as, e.g., at least about 15 N. Again, it is preferred that the tablet contain 100% of the silica or silica derivative.

In a specific embodiment, the solid material fulfils all tests. Thus, the silica or silica derivative - when tested as described herein -

i) has an oil threshold value of at least about 10%, such as, e.g., at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 60%,
ii) has a bulk density of from about 15 to about 30 g/100 ml such as, e.g. from about 17 to about 28 g/100ml, from about 19 to about 25 g/100 ml, from about 20 to about 25 g/100 ml, from about 20 to about 23 g/ml such as about 21 g/100 ml,
iii) releases at least about 30% such as, e.g., at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75% or at least about 80% of an oil, and
iv) in the form of a tablet has a disintegration time of at the most 1 hour such as at the most about 50 min, at the most about 40 min, at the most about 30 min, at the most about 20 min, at the most about 10 min or at the most about 5 min, when tested according to Ph. Eur. Disintegration test, the tablet containing about 90% w/w or more, such as, e.g., about 92.5% w/w or more, about 95% w/w or more, about 97.5% w/w or more or about 100% of the silica or silica derivative, and
v) in the form of a tablet has a tablet hardness of at least about 10 N when tested as described herein.

Other specific embodiments of the invention are those, wherein

the solid pharmaceutical material - when tested as described herein -
i) has an oil treshold value of at least about 55%;

the solid pharmaceutical material - when tested as described herein -
ii) releases at least about 75% of an oil; and/or

the solid pharmaceutical material - when tested as described herein -

iii) in the form of a tablet has disintegration time of at the most about 10 min, when tested according to Ph. Eur. Disintegration test, the tablet containing about 97.5% w/w of the pharmaceutically acceptable material.

The solid pharmaceutically acceptable material for use according to the invention is normally a particulate material in the form of e.g. powders, particles, granules, granulates etc.

In a specific embodiment the silica or silica derivative is a granulated fumed silica or silica derivative.

Moreover, the silica or silica derivative is at the most partly present in precipitated form, or the silica or silica derivative is not present in precipitated form.

Furthermore, the silica or silica derivative normally has an oil absorption value of at least about 100 g oil/100 g such as, e.g., at least about 150 g oil/100 g, at least about 200 g oil/100g, at least about 250 g oil/100 g, at least about 300 g oil/100 g or at least about 400 g oil/100 g silica or silica derivative. The oil absorption value is determined as described in the experimental section herein.

The present inventors have found that a common feature of some of the materials suitable for use as oil sorption material is that they have a relatively large surface area. Accordingly, the silica or silica derivative for use as an oil sorption material according to the invention may have a BET surface area of at least 5 m^2/g such as, e.g., at least about 25 m^2/g, at least about 50 m^2/g, at least about 100 m^2/g, at least about 150 m^2/g, at least about 200 m^2/g, at least about 250 m^2/g or at least about 275 m^2/g.

As mentioned above one of the characteristic features of a pharmaceutically acceptable material for use as an oil sorption material according to the invention is that it retains a good flowability even if it has been loaded with oil or an oily-like material. Thus, the flowability of the pharmaceutically acceptable material loaded with 25% w/w or more such as, e.g. 30% w/w or more, 40% w/w or more, 45% w/w or more, 50% w/w or more, 55% w/w or more, 60% w/w or more, 65% w/w or more or about 70% w/w viscoleo will normally meet the Ph. Eur. requirements.

Moreover, the silica or silica derivative in itself fulfils the test mentioned herein under Threshold Test, but without any addition of viscoleo.

Usually it is preferred to use material having a relatively small particle size because small particles have a higher surface to mass ratio, and therefore small particles will usually be able to support higher amount of oil or oily-like material per mass unit. However, if the particle size is very low the agglomeration process may be difficult to control.

The particle size of the silica or silica derivative may according to the invention be selected among wide limits. According to the invention silicon dioxide materials may be used having median particle sizes in the range of 2-400 μm, preferably in the range of 5-250 μm, more preferred in the range of 10-200 μm, even more preferred in the range of 10-100 μm, and most preferred in the range of 20-30 μm.

The inventors have found that pharmaceutically acceptable expients that fulfil one or more of the requirements mentioned above can be selected from the group consisting of silica acid or a derivative or salt thereof including silicates, silicon dioxide and polymers thereof; silica silylates, silica dimethylsilylates, magnesium aluminosilicate and/or magnesium aluminometasilicate, bentonite, kaolin, magnesium trisilicate, montmorillonite and/or saponite.

In a specific embodiment, the pharmaceutically acceptable material comprises silica acid or a derivative or salt thereof such as, e.g., silicon dioxide or a polymer thereof.

In a further specific embodiment, the pharmaceutically acceptable material is a silicon dioxide product that has properties corresponding to Aeroperl® such as, Aeroperl® 300 and Aeroperl® R 806/30 (silica silylate) (available from Degussa, Frankfurt, Germany).

As it appears from the examples herein, a very suitable material is Aeroperl® 300 (including materials with properties like or corresponding to those of Aeroperl® 300).

An oil sorption material according to the invention is very advantageous for use in the preparation of pharmaceutical, cosmetic, nutritional and/or food compositions, wherein the composition comprises oil or an oily-like material. One of the advantages is that is it possible to incorporate a relatively large amount of oil and oily-like material and still have a material that is solid. Thus, it is possible to prepare solid compositions with a relatively

high load of oil or oily-like materials by use of an oil sorption material according to the invention. As mentioned herein before, within the pharmaceutical field it is an advantage to be able to incorporate a relatively large amount of an oil or an oily-like material in a solid composition especially in those situation where the active substance does not have suitable properties with respect to water solubility (e.g. poor water solubility), stability in aqueous medium (i.e. degradation occurs in aqueous medium), oral bioavailability (e.g. low bioavailability) etc., or in those situations where it is desired to modify the release of an active substance from a composition in order to obtain a controlled, delayed, sustained and/or pulsed delivery of the active substance. Thus, in a specific embodiment it is used in the preparation of pharmaceutical compositions.

The oil sorption material for use in the further processing into solid composition normally absorbs about 5% w/w or more, such as, e.g., about 10% w/w or more, about 15% w/w or more, about 20% w/w or more, about 25% w/w or more, about 30% w/w or more, about 35% w/w or more, about 40% w/w or more, about 45% w/w or more, about 50 w/w or more, about 55% w/w or more, about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more, about 80% w/w or more, about 85% w/w or more, about 90% w/w or more or about 95% w/w or more of an oil or an oily material and is still a solid material.

The compositions may be in the form of particulate materials, granules, pellets, microspheres, nanoparticles or in the form of oral dosage forms including tablets, sachets, capsules.

Normally, the oral dosage form is intended for administration via the oral, buccal or sublingual administration route.

In a further aspect, the invention relates to a solid pharmaceutical particulate material or a pharmaceutical composition comprising

i) an oil or an oily-like material, and

ii) a silica or silica derivative as defined herein (oil sorption material),

wherein the concentration of the oil or oily-like material in the particulate material is about 5% w/w or more such as, e.g., about 10% w/w or more, about 15% w/w or more, about 20% w/w or more, about 25% w/w or more, about 30% w/w or more, about 35% w/w or more, about 40% w/w or more, about 45% w/w or more, about 50 w/w or more, about 55% w/w or more, about 60% w/w or more, about 65% w/w or more, about 70% w/w or more,

preferred in the range of 50-70% by weight.

The particulate material or composition according to the invention also be coated with a film coating, an enteric coating, a modified release coating, a protective coating, an anti-adhesive coating etc.

Suitable coating materials are e.g. methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, acrylic polymers, ethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinylalcohol, sodium carboxymethylcellulose, cellulose acetate, cellulose acetate phthalate, gelatin, methacrylic acid copolymer, polyethylene glycol, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax, zein.

Plasticizers and other ingredients may be added in the coating material. The same or different active substance may also be added in the coating material.

In the present context the term "Oils and oily-like materials" is used in a very broad sense including oils, waxes, semi-solid materials and materials that normally are used as solvents (such as organic solvents) or cosolvents within the pharmaceutical industry, and the term also includes therapeutically and/or prophylactically active substances that are in liquid form at ambient temperature; furthermore the term includes emulsions like e.g. microemulsions and nanoemulsions and suspensions. The oils and oily-like materials that can be absorbed by a material according the invention will normally be liqiuid at ambient or elevated temperature (for practical reasons the max. temperature is about 250 °C). The may be hydrophilic, lipophilic, hydrophobic and/or amphiphilic materials.

The oils and oily-like material that are suitable for use in the present context are substances or materials, which have a melting point of at least about 0 °C and at the most about 250 °C.

In specific embodiments of the invention, the oil or oily-like material has a melting point of about 5 °C or more such as, e.g., about 10 °C or more, about 15 °C or more, about 20 °C or more or about 25 °C or more.

In further embodiments of the invention, the oil or oily-like material has a melting point of at least about 25 °C such as, e.g., at least about 30 °C at least about 35 °C or at least about 40 °C. For practical reasons, the melting point may normally not be too high, thus,

the oil or oily-like material normally has a melting point of at the most about 300 °C such as, e.g., at the most about 250 °C, at the most about 200 °C, at the most about 150 °C or at the most about 100 °C. If the melting point is higher a relatively high temperature may promote e.g. oxidation or other kind of degradation of an active substance in those cases where e.g. a therapeutically and/or prophylactically active substance is included. To this end it should be noted that an oil or oily-like material when used the context of pharmaceuticals is intended to denote a pharmaceutically inert material. The term "inert" is intended to mean that the material in question does not have any therapeutic activity, i.e. it is not a therapeutically, prophylactically and/or diagnostically active substance. Furthermore, the term normally is intended to mean that the material in question does not participate in any chemical reaction with other constituents such as, e.g., the silica or silica derivatives.

In the present context, the melting point is determined by DSC (Differential Scanning Calorimetry). The melting point is determined as the temperature at which the linear increase of the DSC curve intersects the temperature axis (see Fig. 1 for further details).

Interesting oils or oily-like materials are generally substances, which are used in the manufacture of pharmaceuticals as so-called melt binders or solid solvents (in the form of solid dosage form), or as co-solvents or ingredients in pharmaceuticals for topical use.

It may be hydrophilic, hydrophobic and/or have surface-active properties. In general hydrophilic and/or hydrophobic oils or oily-like materials are suitable for use in the manufacture of a pharmaceutical composition comprising a therapeutically and/or prophylactically active substance that has a relatively low aqueous solubility and/or when the release of the active substance from the pharmaceutical composition is designed to be immediate or non-modified. Hydrophobic oil or oily-like materials, on the other hand, are normally used in the manufacture of a modified release pharmaceutical composition. The above-given considerations are simplified to illustrate general principles, but there are many cases where other combinations of oils or oily-like materials and other purposes are relevant and, therefore, the examples above should not in any way limit the invention.

Typically, a suitable hydrophilic oil or oily-like material is selected from the group consisting of: polyether glycols such as, e.g., polyethylene glycols, polypropylene glycols; polyoxyethylenes; polyoxypropylenes; poloxamers and mixtures thereof, or it may be selected from the group consisting of: xylitol, sorbitol, potassium sodium tartrate, sucrose tribehenate, glucose, rhamnose, lactitol, behenic acid, hydroquinon monomethyl ether,

sodium acetate, ethyl fumarate, myristic acid, citric acid, Gelucire 50/13, other Gelucire types such as, e.g., Gelucire 44/14 etc., Gelucire 50/10, Gelucire 62/05, Sucro-ester 7, Sucro-ester 11, Sucro-ester 15, maltose, mannitol and mixtures thereof.

A suitable hydrophobic oil or oily-like material may be selected from the group consisting of: straight chain saturated hydrocarbons, sorbitan esters, paraffins; fats and oils such as e.g., cacao butter, beef tallow, lard, polyether glycol esters; higher fatty acid such as, e.g. stearic acid, myristic acid, palmitic acid, higher alcohols such as, e.g., cetanol, stearyl alcohol, low melting point waxes such as, e.g., glyceryl monostearate, hydrogenated tallow, myristyl alcohol, stearyl alcohol, substituted and/or unsubstituted monoglycerides, substituted and/or unsubstituted diglycerides, substituted and/or unsubstituted triglycerides, yellow beeswax, white beeswax, carnauba wax, castor wax, japan wax, acetylate monoglycerides; NVP polymers, PVP polymers, acrylic polymers, or a mixture thereof.

In an interesting embodiment, the oil or oily-like material is a polyethylene glycol having an average molecular weight in a range of from about 400 to about 35,000 such as, e.g., from about 800 to about 35,000, from about 1,000 to about 35,000 such as, e.g., polyethylene glycol 1,000, polyethylene glycol 2,000, polyethylene glycol 3,000, polyethylene glycol 4,000, polyethylene glycol 5,000, polyethylene glycol 6000, polyethylene glycol 7,000, polyethylene glycol 8,000, polyethylene glycol 9,000 polyethylene glycol 10,000, polyethylene glycol 15,000, polyethylene glycol 20,000, or polyethylene glycol 35,000. In certain situations polyethylene glycol may be employed with a molecular weight from about 35,000 to about 100,000.

In another interesting embodiment, the oil or oily-like material is polyethylene oxide having a molecular weight of from about 2,000 to about 7,000,000 such as, e.g. from about 2,000 to about 100,000, from about 5,000 to about 75,000, from about 10,000 to about 60,000, from about 15,000 to about 50,000, from about 20,000 to about 40,000, from about 100,000 to about 7,000,000 such as, e.g., from about 100,000 to about 1,000,000, from about 100,000 to about 600,000, from about 100,000 to about 400,000 or from about 100,000 to about 300,000.

In another embodiment, the oil or oily-like material is a poloxamer such as, e.g. Poloxamer 188, Poloxamer 237, Poloxamer 338 or Poloxamer 407 or other block copolymers of ethylene oxide and propylene oxide such as the Pluronic® and/or Tetronic® series. Suitable block copolymers of the Pluronic® series include polymers having a molecular

weight of about 3,000 or more such as, e.g. from about 4,000 to about 20,000 and/or a viscosity (Brookfield) from about 200 to about 4,000 cps such as, e.g., from about 250 to about 3,000 cps. Suitable examples include Pluronic® F38, P65, P68LF, P75, F77, P84, P85, F87, F88, F98, P103, P104, P105, F108, P123, F123, F127, 10R8, 17R8, 25R5, 25R8 etc. Suitable block copolymers of the Tetronic® series include polymers having a molecular weight of about 8,000 or more such as, e.g., from about 9,000 to about 35,000 and/or a viscosity (Brookfield) of from about 500 to about 45,000 cps such as, e.g., from about 600 to about 40,000. The viscosities given above are determined at 60 °C for substances that are pastes at room temperature and at 77 °C for substances that are solids at room temperature.

The oil or oily-like material may also be a sorbitan ester such as, e.g., sorbitan di-isostearate, sorbitan dioleate, sorbitan monolaurate, sorbitan monoisostearate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, sorbitan sesqui-isostearate, sorbitan sesquioleate, sorbitan sesquistearate, sorbitan tri-isostearate, sorbitan trioleate, sorbitan tristearate or mixtures thereof.

The oil or oily-like material may of course comprise a mixture of different oils or oily-like materials such as, e.g., a mixture of hydrophilic and/or hydrophobic materials.

Other suitable oils or oily-like materials may be solvents or semi-solid excipients like, e.g. propylene glycol, polyglycolised glycerides including Gelucire 44/14, complex fatty materials of plant origin including theobroma oil, carnauba wax, vegetable oils like e.g. almond oil, coconut oil, corn oil, cottonseed oil, sesame oil, soya oil, olive oil, castor oil, palm kernels oil, peanut oil, rape oil, grape seed oil etc., hydrogenated vegetable oils such as, e.g. hydrogenated peanut oil, hydrogenated palm kernels oil, hydrogenated cottonseed oil, hydrogenated soya oil, hydrogenated castor oil, hydrogenated coconut oil; natural fatty materials of animal origin including beeswax, lanolin, fatty alcohols including cetyl, stearyl, lauric, myristic, palmitic, stearic fatty alcohols; esters including glycerol stearate, glycol stearate, ethyl oleate, isopropyl myristate; liquid interesterified semi-synthetic glycerides including Miglycol 810/812; amide or fatty acid alcolamides including stearamide ethanol, diethanolamide of fatty coconut acids, acetic acid esters of mono and di-glycerides, citric acid esters of mono and di-glycerides, lactic acid esters of mono and diglycerides, mono and di-glycerides, poly-glycerol esters of fatty acids, poly-glycerol poly-ricinoleate, propylene glycol esters of fatty acids, sorbitan monostearates, sorbitan tristearates, sodium stearoyl lactylates, calcium stearoyl lactylates, diacetyl tartaric acid esters of mono and di-glycerides etc.

Pharmaceutically acceptable excipients

A solid pharmaceutical particulate material or a pharmaceutical composition according to the invention may further comprise a pharmaceutically acceptable excipient.

In the present context the terms "pharmaceutically acceptable excipient" are intended to denote any material, which is inert in the sense that it substantially does not have any therapeutic and/or prophylactic effect *per se*. Such an excipient may be added with the purpose of making it possible to obtain a pharmaceutical, cosmetic and/or foodstuff composition, which have acceptable technical properties.

Examples on suitable excipients for use a particular material or composition according to the invention include fillers, diluents, disintegrants, binders, lubricants etc. or mixture thereof. As the particulate material or composition according to the invention may be used for different purposes, the choice of excipients is normally made taken such different uses into considerations. Other pharmaceutically acceptable excipients for suitable use are e.g. acidifying agents, alkalizing agents, preservatives, antioxidants, buffering agents, chelating agents, coloring agents, complexing agents, emulsifying and/or solubilizing agents, flavors and perfumes, humectants, sweetening agents, wetting agents etc.

Examples on suitable fillers, diluents and/or binders include lactose (e.g. spray-dried lactose, α-lactose, β-lactose, Tabletose®, various grades of Pharmatose®, Microtose® or Fast-Floc®), microcrystalline cellulose (various grades of Avicel®, Elcema®, Vivacel®, Ming Tai® or Solka-Floc®), hydroxypropylcellulose, L-hydroxypropylcellulose (low substituted), hydroxypropyl methylcellulose (HPMC) (e.g. Methocel E, F and K, Metolose SH of Shin-Etsu, Ltd, such as, e.g. the 4,000 cps grades of Methocel E and Metolose 60 SH, the 4,000 cps grades of Methocel F and Metolose 65 SH, the 4,000, 15,000 and 100,000 cps grades of Methocel K; and the 4,000, 15,000, 39,000 and 100,000 grades of Metolose 90 SH), methylcellulose polymers (such as, e.g., Methocel A, Methocel A4C, Methocel A15C, Methocel A4M), hydroxyethylcellulose, sodium carboxymethylcellulose, carboxymethylene, carboxymethylhydroxyethylcellulose and other cellulose derivatives, sucrose, agarose, sorbitol, mannitol, dextrins, maltodextrins, starches or modified starches (including potato starch, maize starch and rice starch), calcium phosphate (e.g. basic calcium phosphate, calcium hydrogen phosphate, dicalcium phosphate hydrate), calcium sulfate, calcium carbonate, sodium alginate, collagen etc.

Specific examples of diluents are e.g. calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, microcrystalline cellulose, powdered cellulose, dextrans, dextrin, dextrose, fructose, kaolin, lactose, mannitol, sorbitol, starch, pregelatinized starch, sucrose, sugar etc.

Specific examples of disintegrants are e.g. alginic acid or alginates, microcrystalline cellulose, hydroxypropyl cellulose and other cellulose derivatives, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, starch, pregelatinized starch, carboxymethyl starch (e.g. Primogel® and Explotab®) etc.

Specific examples of binders are e.g. acacia, alginic acid, agar, calcium carrageenan, sodium carboxymethylcellulose, microcrystalline cellulose, dextrin, ethylcellulose, gelatin, liquid glucose, guar gum, hydroxypropyl methylcellulose, methylcellulose, pectin, PEG, povidone, pregelatinized starch etc.

Glidants and lubricants may also be included in the second composition. Examples include stearic acid, magnesium stearate, calcium stearate or other metallic stearate, talc, waxes and glycerides, light mineral oil, PEG, glyceryl behenate, colloidal silica, hydrogenated vegetable oils, corn starch, sodium stearyl fumarate, polyethylene glycols, alkyl sulfates, sodium benzoate, sodium acetate etc.

Other excipients which may be included in the particulate material or composition are e.g. flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, anti-oxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents, absorption enhancing agents, agents for modified release etc.

Other additives in a particulate material or in a composition according to the invention may be antioxidants like e.g. ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, monothioglycerol, potassium metabisulfite, propyl gallate, sodium formaldehylde sulfoxylate, sodium metabisulfite, sodium thiosulfate, sulfur dioxide, tocopherol, tocopherol acetate, tocopherol hemisuccinate, TPGS or other tocopherol derivatives, etc. The carrier composition may also contain e.g. stabilising agents. The concentration of an antioxidant and/or a stabilizing agent in the carrier composition is normally from about 0.1 % w/w to about 5% w/w.

Active substances

A solid pharmaceutical particulate material or a composition according to the invention may further comprise a therapeutically, prophylactically and/or diagnostically active substance.

In a preferred embodiment of the invention a particulate material or composition according to the invention comprises a therapeutically and/or prophylactically active substance. The particulate matter or composition may also or alternatively comprise a cosmetically active substance (i.e. a substance that is employed in cosmetic compositions).

In the present context a therapeutically and/or prophylactically active substance includes any biologically and/or physiologically active substance that has a function on an animal such as, e.g. a mammal like a human. The term includes drug substances, hormones, genes or gene sequences, antigen- comprising material, proteins, peptides, nutrients like e.g. vitamins, minerals, lipids and carbohydrates and mixtures thereof. Thus, the term includes substances that have utility in the treatment and/or preventing of diseases or disorders affecting animals or humans, or in the regulation of any animal or human physiological condition. The term also includes any biologically active substance which, when administered in an effective amount, has an effect on living cells or organisms.

Examples on active substances suitable for use in a particulate material or composition according to the invention are in principle any active substance such as, e.g. freely water soluble as well as more slightly or insoluble active substances. Thus, examples on active substances suitable for use are e.g. antibacterial substances, antihistamines and decongestants, anti-inflammatory agents, antiparasitics, antivirals, local anesthetics, antifungals, amoebicidals or trichomonocidal agents, analgesics, antianxiety agents, anticlotting agents, antiarthritics, antiasthmatics, antiarthritic, anticoagulants, anticonvulsants, antidepressants, antidiabetics, antiglaucoma agents, antimalarials, antimicrobials, antineoplastics, antiobesity agents, antipsychotics, antihypertensives, antitussives, auto-immune disorder agents, anti-impotence agents, anti-Parkinsonism agents, anti-Alzheimers' agents, antipyretics, anticholinergics, anti-ulcer agents, anorexic, beta-blockers, beta-2 agonists, beta agonists, blood glucose-lowering agents, bronchodilators, agents with effect on the central nervous system, cardiovascular agents, cognitive enhancers, contraceptives, cholesterol-reducing agents, cytostatics, diuretics, germicidals, H-2 blockers, hormonal agents, hypnotic agents, inotropics, muscle relaxants, muscle contractants, physic energizers, sedatives, sympathomimetics, vasodilators, vasoconstrictors, tranquilizers, electrolyte supplements, vitamins,

counterirritants, stimulants, anti-hormones, drug antagonists, lipid-regulating agents, uricosurics, cardiac glycosides, expectorants, purgatives, contrast materials, radiopharmaceuticals, imaging agents, peptides, enzymes, growth factors, etc.

Specific examples include e.g.

Anti-inflammatory drugs like e.g. ibuprofen, indometacin, naproxen, nalophine;

Anti-Parkinsonism agents like e.g. bromocriptine, biperidin, benzhexol, benztropine etc.

Antidepressants like e.g. imipramine, nortriptyline, pritiptyline, etc.

Antibiotics like e.g. clindamycin, erythomycin, fusidic acid, gentamicin, mupirocine, amfomycin, neomycin, metronidazol, sulphamethizole, bacitracin, framycetin, polymyxin B, acitromycin etc,

Antifungal agents like e.g. miconazol, ketoconaxole, clotrimazole, amphotericin B, nystatin, mepyramin, econazol, fluconazol, flucytocine, griseofulvin, bifonazole, amorofine, mycostatin, itraconazole, terbenafine, terconazole, tolnaftate etc.

Antimicrobial agents like e.g.metronidazole, tetracyclines, oxytetracylines, peniciilins etc.

Antiemetics like e.g. metoclopramide, droperidol, haloperidol, promethazine etc.

Antihistamines like e.g. chlorpheniramine, terfenadine, triprolidine etc.

Antimigraine agents like e.g. dihydroergotamine, ergotamine, pizofylline etc.

Coronary, cerebral or peripheral vasodilators like e.g. nifedipine, diltiazem etc.

Antianginals such as, e.g., glyceryl nitrate, isosorbide dinitrate, molsidomine, verapamil etc.

Calcium channel blockers like e.g. verapamil, nifedipine, diltiazem, nicardipine etc.

Hormonal agents like e.g. estradiol, estron, estriol, polyestradiol, polyestriol, dienestrol, diethylstilbestrol, progesterone, dihydroprogesterone, cyprosterone, danazol, testosterone etc.

Contraceptive agents like e.g. ethinyl estradiol, lynestrenol, etynodiol, norethisterone, mestranol, norgestrel, levonorgestrel, desodestrel, medroxyprogesterone etc.

Antithrombotic agents like e.g. heparin, warfarin etc.

Diuretics like e.g. hydrochlorothiazide, flunarizine, minoxidil etc.

Antihypertensive agents like e.g. propanolol, metoprolol, clonidine, pindolol etc.

Corticosteroids like e.g. beclomethasone, betamethasone, betamethasone-17-valerate, betamethasone-dipropionate, clobetasol, clobetasol-17-butyrate, clobetasol-propionate, desonide, desoxymethasone, dexamethasone, diflucortolone, flumethasone, flumethasone-pivalte, fluocinolone acetonide, fluocinoide, hydrocortisone, hydrocortisone-17-butyrate, hydrocortisonebuteprate,methylprednisolone, triamcinolone acetonide, hacinonide, fluprednide acetate, alklometasone-dipropionate, fluocortolone, fluticason-propionte, mometasone-furate, desoxymethasone, diflurason-diacetate, halquinol, cliochinol, chlorchinaldol, fluocinolone-acetonide etc.

Dermatological agents like e.g. nitrofurantoin, dithranol, clioquinol, hydroxyquinoline, isotretionin, methoxsalen, methotrexate, tretionin, trioxalen, salicylic acid, penicillamine etc.

Steroids like e.g. estradiol, progesterone, norethindrone, levonorgestrel, ethynodiol, levonorgestrol, norgestimate, gestanin, desogestrel, 3-keton-desogesterel, demegestone, promethoestrol, testosterone, spironolactone and esters thereof etc.

Nitro compounds like e.g. amyl nitrates, nitroglycerine and isosorbide nitrate etc.

Opioids like e.g. morphine, buprenorphine, oxymorphone, hydromorphone, codeine, tramadol etc.

Prostaglandins such as, e.g., a member of the PGA, PGB, PGE or PGF series such as, e.g. minoprostol, dinoproston, carboprost, eneprostil etc.

Peptides like e.g. growth hormone releasing factors, growth factors (e.g. epidermal growth factor (EGF), nerve growth factor (NGF), TGF, PDGF, insulin growth factor (IGF), fibroblast growth factor (aFGF, bFGF etc.), somatostatin, calcitonin, insulin, vasopressin, interferons, IL-2 etc., urokinase, serratiopeptidase, superoxide dismutase, thyrotropin releasing hormone, lutenizing hormone releasing hormone (LH-RH), corticotrophin releasing hormone, growth hormone releasing hormone (GHRH), oxytocin, erythropoietin (EPO), colony stimulating factor (CSF) etc.

Interesting examples are also prescription drugs like:

Cardiovascular drugs
Zocor®
Lipitor®
Prevachol®
Mevalotin®
Mevacor®
Lescol®
TriCor®
Norvasc®
Cozaar and Hyzaar®
Prinivil and Prinzide®
Diovan®/Co-Diovan®
Zestril®
Vasotech® and Vaseretic®
Lotensin®/Cibacen® and Lotrel®
Adalat®
Toprol-XL®/Seloken®
Tritace®/Delix®
Accupril® and Accuretic®
Avapro® and Avalide®
Plendil®
Monopril®
Blopress®
Atacand®
Tenormin®
Avapro®/Aprovel®

Coreg®

Altace®

Capoten®

Plavix®

Lovenox®/Clexane®

Fraxiparine®

ReoPro®

Panaldine®

Cordarone®

Central nervous system drugs

Paxil/Seroxat®

Zolotoft®

Prozac®, Prozac Weekly® and Sarafem®

Effexor®

Wellbutrin®

Celexa®

Remeron®

Serzone®

Zyprexa®

Risperdal®

Seroquel®

Clozaril®/Leponex®

Neurontin®

Depaktoke®

Lamictal® Topamax®

Tegretol®

Imitrex®/Imigran®

Zomig®

Maxalt®

Ambien®

Stilnox®

Ultane®/Sevorane®

Diprivan®

BuSpar®

Xanax®

Aricept®

Memantine®

Adderall®

Dystonia®

Botox®

Anti-infective agents

Augmentin®

Cipro®/Ciprobay®

Zithromax®

Biaxin®

Levaquin® and Floxin®

Rocephin®

Primaxin®

Ceftin®/Zinnat®

Cravit®

Zosyn®/Tazocin®

Cefzil®

Tequin®

Tortaz®/Fortum®

Combivir®

Zerit®

Valtrex®

Epivir®

Zovirax®

Crixivan®

Viracept®

Viramune®

Kaletra®

Diflucan®

Lamisil®

Sporanox®

Respiratory drugs

ClaritinAllegra®Telfast®

Zyrtec®

Flonase®/Flixonase®

Atrovent®

Nasonex®

Rhinocort®

Alesion®

Singulair®

Flovent®/Flixotide®

Advair®/Seretide®

Serevent®

Pulmicort®

Ventoline®

Combivent®

Synagis®

Mucosolvan®

Gastrointestinal drugs

Prilosec®/Losec®

Prevacid®

Gaster®

Takepron®

Zantac®

Pantozol Nexium Protonix®

Aciphex®/Pariet®

Pepcid®

Axid®

Zoton®

Zofran®

Cancer drugs

Taxol®

Taxotere®

Nolvadex®

Herceptin Ellence®/Pharmorubicin®

Lupron®

Zoladex®

Leuplin®

Casodex®

Intron A®, Peg-Intron® and Rebertron®

Rituxan®

Gemzar®
Paraplatin®
Camptosar®

Antiarthritic drugs/analgesics
Celebrex®
Vioxx®
Enbrel®
Remicade®
Voltaren®
Mobic®

Duragesic®
Ultram ®and Ultrcet®

Blood disorder treatments
Procrit®/Eprex®
Epogen®
Epogin®
NeoRecormon®
Neupogen®
NovoSeven®

Diabetes drugs
Glucophage®
Humulin Avandia®
Humalog®
Actos®
Amaryl®
Glucovance®
Glucophage XR®
Glucotrol XL®
Precose®/Glucobay®

Bone metabolism regulators
Fosamax®
Evista®

Miacalcin®

Actone®l

Aredia®

Urinary disorder agents

Harnal®

Proscar®

Cardura®

Flomax®

Detrol®

Hormones

Premarin®, Premphase® And prempro®

Estraderm®

Synthroid®

Immunosuppressive agents

Neoral®/Sandimmun®

CellCept

Rapamune®®

Prograf®

Medrol®

Multiple Sclerosis drugs

Avonex®

Betaseron®/Betaferon®

Rebif®

Copaxone®

Biologicals

Prevnar®

Engerix-B®

Infanrix®

Gamimune N®

Sexual dysfunction drugs

Viagra®

Imaging agents

Iopamiron®

Omnipaque®

Magnevist®

Ophthalmic drugs

Xalatan®

Trusopt® and Cosopt®

Dermatological drugs

Accutane®/Roaccutan®

Cleocin®

Growth failure therapies

Genotropin®

Humatrope®

Infertility drugs

Gonal-F®

Follistim(Puregon®

Gaucher disease drugs

Cerezyme®

Obesity drugs

Xencial®

Acromegaly drugs

Sandostatin®

Contraceptives

Depo-Provera®

Other interesting examples of active substances that are slightly soluble, sparingly soluble or insoluble in water are given in the following tables:

Table 1

Poorly-Soluble

Drug Candidates

Drug Name	Therapeutic Class	Solubility In Water
Alprazolam	CNS	Insoluble
Amiodarone	Cardiovascular	Very Slightly
Amlodipine	Cardiovascular	Slightly
Astemizole	Respiratory	Insoluble
Atenolol	Cardiovascular	Slightly
Azathioprine	Anticancer	Insoluble
Azelastine	Respiratory	Insoluble
Beclomethasone	Respiratory	Insoluble
Budesonide	Respiratory	Sparingly
Buprenorphine	CNS	Slightly
Butalbital	CNS	Insoluble
Carbamazepine	CNS	Insoluble
Carbidopa	CNS	Slightly
Cefotaxime	Anti-infective	Sparingly
Cephalexin	Anti-infective	Slightly
Cholestyramine	Cardiovascular	Insoluble
Ciprofloxacin	Anti-infective	Insoluble
Cisapride	Gastrointestinal	Insoluble
Cisplatin	Anticancer	Slightly
Clarithromycin	Anti-infective	Insoluble
Clonazepam	CNS	Slightly
Clozapine	CNS	Slightly

(continued)

Drug Name	Therapeutic Class	Solubility In Water
Cyclosporin	Immunosuppressant	Practically Insoluble
Diazepam	CNS	Slightly
Diclofenac sodium	NSAID	Sparingly
Digoxin	Cardiovascular	Insoluble
Dipyridamole	Cardiovascular	Slightly
Divalproex	CNS	Slightly
Dobutamine	Cardiovascular	Sparingly
Doxazosin	Cardiovascular	Slightly
Enalapril	Cardiovascular	Sparingly
Estradiol	Hormone	Insoluble
Etodolac	NSAID	Insoluble
Etoposide	Anticancer	Very Slightly
Famotidine	Gastrointestinal	Slightly
Felodipine	Cardiovascular	Insoluble
Fentanyl citrate	CNS	Sparingly
Fexofenadine	Respiratory	Slightly
Finasteride	Genito-urinary	Insoluble
Fluconazole	Antifungal	Slightly
Flunosolide	Respiratory	Insoluble
Flurbiprofen	NSAID	Slightly
Fluvoxamine	CNS	Sparingly
Furosemide	Cardiovascular	Insoluble
Glipizide	Metabolic	Insoluble
Glyburide	Metabolic	Sparingly
Ibuprofen	NSAID	Insoluble
Isosorbide dinitrate	Cardiovascular	Sparingly
Isotretinoin	Dermatological	Insoluble
Isradipine	Cardiovascular	Insoluble
Itraconzole	Antifungal	Insoluble

(continued)

Drug Name	Therapeutic Class	Solubility In Water
Ketoconazole	Antifungal	Insoluble
Ketoprofen	NSAID	Slightly
Lamotrigine	CNS	Slightly
Lansoprazole	Gastrointestinal	Insoluble
Loperamide	Gastrointestinal	Slightly
Loratadine	Respiratory	Insoluble
Lorazepam	CNS	Insoluble
Lovastatin	Cardiovascular	Insoluble
Medroxyprogesterone	Hormone	Insoluble
Mefenamic acid	Analgesic	Slightly
Methylprednisolone	Steroid	Insoluble
Midazolam	Anesthesia	Insoluble
Mometasone	Steroid	Insoluble
Nabumetone	NSAID	Insoluble
Naproxen	NSAID	Insoluble
Nicergoline	CNS	Insoluble
Nifedipine	Cardiovascular	Practically Insoluble
Norfloxacin	Anti-infective	Slightly
Omeprazole	Gastrointestinal	Slightly
Paclitaxel	Anticancer	Insoluble
Phenytoin	CNS	Insoluble
Piroxicam	NSAID	Sparingly
Quinapril	Cardiovascular	Insoluble
Ramipril	Cardiovascular	Insoluble
Risperidone	CNS	Insoluble
Saquinavir	Protease inhibitor	Practically insoluble
Sertraline	CNS	Slightly
Simvastatin	Cardiovascular	Insoluble
Terbinafine	Antifungal	Slightly
Terfenadine	Respiratory	Slightly
Triamcinolone	Steroid	Insoluble

Valproic acid	CNS	Slightly
Zolpidem	CNS	Sparingly

Table 2

Poorly-Soluble Drugs with Low Bioavailability

Drug Name	Indication	Solubility In Water	Bioavailability
Astemizole	Allergic Rhinitis	Insoluble	Low - moderate
Cyclandelate	Peripheral vascular disease	Insoluble	Low
Perphenazine	Psychotic disorder	Insoluble	Low
Testosterone	Androgen Replacement Therapy	Insoluble	Low
Famotidine	GERD	Slightly soluble	Low (39-50%)
Budesonide	Allergic Rhinitis	Sparingly soluble	Low (~15%)
Mesalamine	Irritable Bowel Syndrome	Slightly soluble	Low (~20%)
Clemastine fumarate	Allergic Rhinitis	Slightly soluble	Low (~39%)
Buprenorphine	Pain	Slightly soluble	Low (<30%)
Sertraline	Anxiety	Slightly soluble	Low (<44%)
Auranofin	Arthritis	Slightly soluble	Low (15-25%)
Felodipine	Hypertension	Insoluble	Low (15%)
Isradipine	Hypertension	Insoluble	Low (15-24%)
Danazol	Endometriosis	Insoluble	Low
Loratadine	Allergic Rhinitis	Insoluble	Low
Isosorbide dinitrate	Angina	Sparingly soluble	Low (20-35%)
Fluphenazine	Psychotic disorder	Insoluble	Low (2-3%)
Spironolactone	Hypertension, Edema	Insoluble	Low (25%)
Biperiden	Parkinson's disease	Sparingly soluble	Low (29-33%)
Cyclosporin	Transplantation	Slightly soluble	Low (30%)
Norfloxacin	Bacterial Infection	Slightly soluble	Low (30-40%)
Cisapride	GERD	Insoluble	Low (35-40%)
Nabumetone	Arthritis	Insoluble	Low (35%)
Dronabinol	ANTIEMETIC	Insoluble	Low 10-20%)
Lovastatin	Hyperlipidemia	Insoluble	Low (~5%)
Simvastatin	Hyperlipidemia	Insoluble	Low (<5%)

The amount of active substance incorporated in a particulate material (and/or in a pharmaceutical, cosmetic or foodstuff composition) may be selected according to known principles of pharmaceutical formulation. In general, the dosage of the active substance present in a particulate material according to the invention depends *inter alia* on the specific drug substance, the age and condition of the patient and of the disease to be treated.

In a specific embodiment of the invention the therapeutically, prophylactically and/or diagnostically active substance is solid at ambient temperature. It may also at least partly, including totally, be present in the form of a solid dispersion including a solid solution. In the latter case, the active substance may be dispersed or dissolved in the oil or oily-like material.

A particulate material or composition according to the invention may comprise a cosmetically active ingredient and/or a food ingredient. Specific examples include vitamins, minerals, vegetable oils, hydrogenated vegetable oils, etc.

Other aspects of the invention

The invention also relates to a method for the preparation of a pharmaceutical composition comprising about 5% w/w or more such as, e.g., about 10% w/w or more, about 15% w/w or more, about 20% w/w or more, about 25% w/w or more, about 30% w/w or more, about 35% w/w or more, about 40% w/w or more, about 45% w/w or more, about 50 w/w or more, about 55% w/w or more, about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more, about 80% w/w or more, about 85% w/w or more, about 90% w/w or more or about 95% w/w or more of an oil or an oily-like material, the method comprising loading the oil or oily-like material to a pharmaceutically acceptable material defined herein (oil sorption material). The composition is preferably in solid form.

In principle agglomerates according to the invention may be prepared using procedures known within the area for melt agglomeration. Examplary of apparatus, which may be used are low shear mixers, high shear mixers, fluid beds, fluid bed granulators, rotary fluidised beds and drum granulators.

In one embodiment the agglomerate is prepared by melting the oil or oily-like material, dissolving or dispersing the active compound in the melt, and spraying or pouring the melt on the silica or silica derivative. The spraying or pouring step may be performed in

accordance with known procedures.

In another embodiment all constituents of the agglomerate is added to a high shear mixer, optionally provided with a heating jacket. By operating the high shear mixer the friction heat and heat supplied by the heating jacket will melt the vehicle, which subsequently dissolve or disperse the active compound and deposits at a composition comprising the silica or silica derivative.

The loading of the oil sorption material with oil or oily-like material is normally performed by mixing (e.g. mechanically or in fluid-bed or in a spray drier), spraying and/or pouring such as by melt agglomeration or controlled agglomeration techniques.

In a specific embodiment the controlled agglomeration is performed by
i) spraying a first composition in liquid form comprising an oil or an oily-like material on a second composition in solid form comprising a silica or silica derivative as defined in any of claims 1-30, and
ii) mixing or other means of mechanical working the second composition onto which the first composition is sprayed to obtain a pharmaceutical particulate material, which optionally may be further processed to obtain a pharmaceutical dosage form.

In the agglomeration processes the prepared agglomerate may be influenced by several process variables such as temperature of vehicle, filler and heating jacket; the impeller speed, time of treatment etc. The skilled person can using simple routine experiments determine suitable parameters for an intended melt agglomeration process using a given active compound, filler and vehicle, with use of a particular given suitable equipment.

The particulate material in the form of agglomerates according to the invention may be used for the preparation of pharmaceutical compositions for oral administration according to well known procedures. Pharmaceutical compositions may be prepared by mixing a agglomerate with usual pharmaceutical acceptable excipients, followed by preparing the composition using said mixture.

Preferred pharmaceutical composition for oral administration according to the invention are tablets and capsules.

Tablets may be prepared using procedures known as such, such as mixing the agglomerate according to the invention with known excipients usually used for tablets, and

pressing the resulting mixture into tablets. The tablets may or may not be coated according to well known procedures.

Capsules may be prepared using procedures know as such, for example mixing a agglomerate according to the invention with suitable excipients, and filling the mixture into suitable capsules, such as gelatine capsules.

In one specific embodiment a pharmaceutical composition is prepared using a particular material, an agglomerate, according to the invention comprising an active compound and a water soluble oil or oily-like material. The pharmaceutical composition will provide the active compound for fast and high bioavailability of the active compound after ingestion of the pharmaceutical composition.

In another specific embodiment a pharmaceutical composition is prepared using a particulate material, an agglomerate, according to the invention comprising an active compound and a vehicle insoluble in water. The pharmaceutical composition will provide a sustained release of the active compound over a prolonged period of time.

It may even be possible to prepare a pharmaceutical composition comprising two or more different agglomerates. These two or more agglomerates may comprise same active compound but different vehicles, thus providing differing release rates of the active compound from the two or more agglomerates, in order to provide pharmaceutical having a particular desired release profile of the active compound. Alternatively the two or more agglomerates may comprise different active compounds. The skilled person will appreciate that other combinations may be used for providing for a particular desired effect.

The details and particulars disclosed under the main aspect of the invention apply *mutatis mutandis* to the other aspects of the invention.

The invention is further illustrated in the following non-limiting examples.

Methods

Threshold Test

The test involves determination of flowability according to the method described in Ph.Eur. by measuring the flow rate of the material out of a funnel with a nozzle diameter of 10.0 mm.

Viscoleo (medium chain triglycerides MCT; Miglyol 812 N from Condea) was added to 100 g of the solid pharmaceutically acceptable material to be tested for use according to the invention and mixed manually. The mixture obtained was sieved through sieve 0.3 mm to assure a homogenous mixture. The oil was added successively until a flow of 100 g of the mixture could not flow through the nozzle. If the material to be tested has a high bulk volume (e.g. like that of Aeroperl 300) only 50 g of the mixture is used when testing these blends. The maximal concentration of oil where flow of material could be obtained is called the Threshold Value (given as % w/w).

Release Test

A fat-soluble colorant Sudan II (BDH Gur®) obtained from BDH VWR International 14.3 mg was dissolved in 50.0 g viscoleo (fractionated medium chain triglycerides).

10 g of the oil was added to 10.0 g of the solid pharmaceutically acceptable material to be tested for use according to the present invention and mixed until the oil was fully absorbed in the solid material. The mixture was subsequently sieved through sieve 0.3 mm to achieve a homogeneous mixture.

1.00 g of the mixture was transferred to a centrifugal tube and 3.00 ml of water was added. The suspension was mixed in a blood sample turner for 1 hour and subsequently centrifuged for 10 minutes at 5000 rpm. The upper phase of oil and water was transferred carefully to a beaker and the water was evaporated in an oven at 80 °C until constant weight. The amount of oil released from the solid material was calculated on basis of the weight of the remaining after evaporation of the water phase.

Disintegration Test

The disintegration time was determined according to the method described in to Ph. Eur.

Determination of Bulk Density

The bulk density was measured by pouring 100 g of the powder in question in a 250 ml graduated cylinder. The bulk density is given as the tapped bulk density in g/ml. The determination was performed according to Ph. Eur. (apparent volume).

Determination of Oil Absorption Value

The oil absorption value is determined by adding well-defined amounts (a 10 g) of viscoleo to a well-defined amount of the pharmaceutically acceptable material (100 g) to be tested. The oil absorption value (expressed as g viscoleo/100 g material) is reached when a further addition of 10 g oil results in a material that does not have suitable properties with respect to flowability, i.e. the material does not meet the meet the requirements when tested according to Ph.Eur. (flowability test; see above under Threshold Test herein).

Determination of BET Surface Area

The apparatus applied was a Micromertics Gemini 2375. The method applied was according to USP volumetric methods based on multiple point determination.

Determination of Flowability

The flowability was determined according to the method described in Ph.Eur. measuring the flow rate of the material out of a funnel with a nozzle diameter of 10.0 mm.

Determination of weight variation

The tablets prepared in the Examples herein were subject to a test for weight variation performed in accordance with Ph. Eur.

Determination of average tablet hardness

The tablets prepared in the Examples herein were subject to at test for tablet hardness employing Schleuniger Model 6D apparatus and performed in accordance with the general instructions for the apparatus.

Examples

Comparison of Neusilin US2 and Aeroperl 300

1. Absorption of oil and release in water

1.1 Procedures and results

A fat-soluble colorant Sudan II (BDH Gur®) 14.3 mg was dissolved in 50.0 g viscoleo (fractionated medium chain triglycerides).

10 g of the oil was added to 10.0 g Neusilin or Aeroperl respectively and mixed until the oil was fully absorbed in the solid phase. The free flowing powder was subsequently sieved through sieve 0.3 mm to achieve a homogeneous mixture. 1.00 g of the mixture was transferred to a centrifugal tube and 3.00 ml of water was added. The suspension was mixed in a blood sample turner for 1 hour and subsequently centrifuged for 10 minutes at 5000 rpm. The upper phase of oil and water was transferred carefully to a beaker and the water was evaporated in an oven at 80 °C until constant weight. The amount of oil released from the solid material was calculated on basis of the weight of the remaining after evaporation of the water phase. The results are shown in the Table 1. The solid material of Neusilin was strongly red coloured after release of oil to the water phase, whereas the material of Aeroperl was only weakly coloured indicating an almost complete release of oil from the solid phase.

Material	Oil released, %
Neusilin US2	26.8
Neusilin US2	29.8
Aeroperl 300	86.7
Aeroperl 300	84.7

Table 1

1.2 Conclusion

Neusilin US2 releases far less oil into the water phase compared to Aeroperl 300.

2. Comparison of flowability of different pharmaceutical fillers

2.1 Procedures and results

The flowability was determined according to the method described in Ph.Eur. measuring the flow rate of the material out of a funnel with a nozzle diameter of 10.0 mm.

Viscoleo was added to 100 g of the solid material and mixed manually. The material was sieved through sieve 0.3 mm to assure a homogenous mixture. The oil was added successively until a flow of 100 g of the mixture could not flow thorugh the nozzle. Due to the high bulk volume of Aeroperl only 50 g of the mixture was used when testing these blends. The maximal concentration of oil where flow of material could be obtained is shown in Table 2.

Solid material	Oil concentration (threshold for flow)
Aeroperl 300	63%
Neusilin US 2	67%
Di-cafos	4.7%
Lactose DC LAC11	2.9%

Table 2

2.1 Conclusion

Particulate materials such as Aeroperl and Neusilin having a very high specific surface area, BET surface area, (200-300 m^2/g) are able to absorb high amounts of liquid vehicles without loosing flowability as compared to commonly used free flowing tablet fillers such as Di-cafos or lactose.

3. Tabletting characteristics of Aeroperl 300 and Neusilin

3.1 Procedures and results

Circular tablet of 8 mm in diameter (compound cup) was manually compressed on an excentric tabletting machine, TM20, Diaf. The tablets only contained Aeroperl 300 and Neusilin, respectively. The disintegration time was measured according to the procedure in Ph.Eur. and the tablet hardness was estimated using Schleuniger 6D. The results are shown in Table 3.

Material	Tablet weight, mg	Tablet hardness, N	Mean disintegration time, min
Neusilin US 2	100	37	> 60
Aeroperl 300	100	30	2.1

Table 3

3.2 Conclusion

Tablets compressed out of Neusilin show a significantly higher disintegration times compared to Aeroperl 300.

4. Process example using Aeroperl as carrier

4.1 Procedures and results

Gelucire 44/14 (Gattefossé) was sprayed on Aeroperl 300 in a fluid bed Strea-1 using the controlled agglomeration technology described in WO 03/004001.

The melt (Gelucire 44/14) was heated to 70 °C and sprayed on 100 g Aeroperl 300 keeping the product temperature below 35 °C during processing.

The amount of Gelucire applied to Aeroperl corresponded to 72% of total (261 g Gelucire applied to 100 g Aeroperl).

The agglomerated product was mixed with Avicel PH200 in a Turbula mixer and tabletted without addition of glidant. Subsequently the blend was compressed on an excentric tabletting machine Diaf TM20. Tablet diameter was 8 mm (compound cup). The tablet characteristics are shown in Table 4.

Disintegration time and tablet weight variation is determined according to Ph. Eur. The tablet hardness is determined on a Schleuniger 6D.

Avicel conc. %	Mean disintegration time, min	Mean Tablet hardness, N	Mean Tablet weight mg	Weight variation S_{rel}, %
0	25	28	216	0.3
10	32	38	222	0.7
20	22	35	222	1.8
30	14	45	216	0.4

Table 4

4.1 Conclusion

Application of the semisolid Gelucire 44/14 (melting point approx. 35 °C) using Aeroperl 300 as an oil sorption material carrier resulted in satisfactory compression of the product.

The load of Gelucire could be significantly increased (65-75% the load was about 68%) using Aeroperl 300 compared to other conventional fillers. Addition of Avicel as extra granular phase resulted in increasing tablet hardness positively correlated to the concentration of Avicel.

The results also show that it is possible to compress tablets from the material obtained by loading Gelucire on Aeroperl 300 without addition of any excipients.

Comparison Example

Differentiating Aeropearl 300 from Sipernat

Flow properties:

Flow properties of Aeropearl 300 and different qualities of Sipernat are measured through a 10 mm nozzle (PhEur). 100 ml material is used for each measurement.

Material	Batch number	Runtime, sec.	Hammer used to initiate flow
Aeropearl 300	FU-03-014	1	No
Sipernat 50	RD-03-136	Indefinite	Yes
Sipernat 50S	RD-03-137	Indefinite	Yes

Bulk densities:

Bulk density is measured by weighing 100 ml material gently added in a measuring cylinder.

Material	Batch number	Bulk density, g/100 ml
Aeropearl 300	FU-03-014	21,24
Sipernat 50	RD-03-136	10,30
Sipernat 50S	RD-03-137	12,80

Tabletting characteristics

Attempts to compress Sipernat 50S into tablet (Diaf TM20 tablet diameter 8 mm) was unsuccessful due to low bulk density and poor flowability. Tabletting by hand on resulted in tablets with a tablet hardness below 6 N. In comparison tablets of a hardness of 15-30 N could be compressed out of Aeroperl 300.

Conclusion

Sipernat 50 and 50 S differ from Aeroperl in having a lower bulk density g/ml and poor flowability. Further, tablet compression was not possible or resulted in tablets with very low hardness. Accordingly, the Sipernat qualities are not suitable for use according to the present invention.

Claims

1. Use of a silica or silica derivative, which - when tested as described herein -
i) has an oil threshold value of 10% or more, when tested according to the Threshold Test herein,
ii) has a bulk density of at least about 15 g/100 ml,
and at least one of
iii) releases at least 30% of an oil, when tested according to the Release Test herein, and
iv) in the form of a tablet has a disintegration time of at the most 1 hour, when tested according to Ph. Eur. Disintegration test, the tablet containing about 90% w/w or more of the silica or silica derivative,
v) in the form of a tablet has a tablet hardness of at least about 10 N when tested as described herein,
as a sorption material for oils or oily-like materials.

2. Use according to claim 1 as a sorption material for oils or oily-like materials in pharmaceuticals, cosmetics and/or foodstuff.

3. Use according to claim 1 or 2 as a sorption material for oils or oily-like materials in pharmaceuticals.

4. Use according to any of the preceding claims, wherein the silica or silica derivative - when tested as described herein -
i) has an oil threshold value of at least about 15%, such as, e.g., at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, or at least about 45%.

5. Use according to any of the preceding claims, wherein the silica or silica derivative - when tested as described herein -
i) has an oil threshold value of at least about 50%, such as, e.g., at least about 55% or at least about 60%.

6. Use according to any of the preceding claims, wherein the silica or silica derivative - when tested as described herein -
ii) has a bulk density of from about 15 to about 30 g/100 ml such as, e.g. from about 17 to about 28 g/100ml, from about 19 to about 25 g/100 ml, from about 20 to about 25 g/100 ml, from about 20 to about 23 g/ml such as about 21 g/100 ml.

7. Use according to any of the preceding claims, wherein the silica or silica derivative has a tapped density of at least about 20 g/100 ml such as, e.g., at least about 22 g/100 ml, at least about 25 g/100 ml, at least about 26 g/100 ml, at least about 27 g/100 ml.

8. Use according to claim 7, wherein the tapped density is at the most about 40 g/100 ml such as, e.g. at the most about 35 g/100 ml or at the most about 30 g/100 ml.

9. Use according to any of the preceding claims, wherein the silica or silica derivative - when tested as described herein -
ii) releases at least about 30% such as, e.g., at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 60% of an oil.

10. Use according to any of the preceding claims, wherein the silica or silica derivative - when tested as described herein -
ii) releases at least about 65% such as, e.g., at least about 70%, at least about 75% or at least about 80% of an oil.

11. Use according to any of the preceding claims, wherein the silica or silica derivative - when tested as described herein
iv) in the form of a tablet has a disintegration time of at the most 1 hour, when tested according to Ph. Eur. Disintegration test, the tablet containing about 90% w/w or more, such as, e.g., about 92.5% w/w or more, about 95% w/w or more, about 97.5% w/w or more or about 100% of the silica or silica derivative.

12. Use according to any of the preceding claims, wherein the silica or silica derivative - when tested as described herein -
iv) in the form of a tablet has a disintegration time of at the most about 50 min, such as, e.g., at the most about 40 min, at the most about 30 min, at the most about 20 min, at the most about 10 min or at the most about 5 min, when tested according to Ph. Eur. Disintegration test, the tablet containing about 90% w/w or more, such as, e.g., about 92.5% w/w or more, about 95% w/w or more, about 97.5% w/w or more or about 100% of the silica or silica derivative.

13. Use according to any of the preceding claims, wherein the silica or silica derivative - when tested as described herein –

v) in the form of a tablet containing about 90% w/w or more, such as, e.g., about 92.5% w/w or more, about 95% w/w or more, about 97.5% w/w or more or about 100% of the silica or silica derivative has a tablet hardness of at least about 15 N.

14. Use according to any of the preceding claims, wherein the silica or silica derivative - when tested as described herein -

i) has an oil threshold value of at least about 10%, such as, e.g., at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 60%,

ii) has a bulk density of from about 15 to about 30 g/100 ml such as, e.g. from about 17 to about 28 g/100ml, from about 19 to about 25 g/100 ml, from about 20 to about 25 g/100 ml, from about 20 to about 23 g/ml such as about 21 g/100 ml,

iii) releases at least about 30% such as, e.g., at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75% or at least about 80% of an oil, and

iv) in the form of a tablet has a disintegration time of at the most 1 hour such as at the most about 50 min, at the most about 40 min, at the most about 30 min, at the most about 20 min, at the most about 10 min or at the most about 5 min, when tested according to Ph. Eur. Disintegration test, the tablet containing about 90% w/w or more, such as, e.g., about 92.5% w/w or more, about 95% w/w or more, about 97.5% w/w or more or about 100% of the silica or silica derivative, and

v) in the form of a tablet has a tablet hardness of at least about 10 N when tested as described herein.

15. Use according to any of the preceding claims, wherein the solid pharmaceutical material - when tested as described herein -

i) has an oil threshold value of at least about 55%.

16. Use according to any of the preceding claims, wherein the solid pharmaceutical material - when tested as described herein -

ii) releases at least about 75% of an oil.

17. Use according to any of the preceding claims, wherein the solid pharmaceutical material - when tested as described herein -

iii) in the form of a tablet has disintegration time of at the most about 10 min, when tested according to Ph. Eur. Disintegration test, the tablet containing about 97.5% w/w of the pharmaceutically acceptable material.

18. Use according to any of the preceding claims, wherein the solid pharmaceutical material is a particulate material.

19. Use according to any of the preceding claims, wherein the silica or silica derivative is a granulated fumed silica or silica derivative.

20. Use according to any of the preceding claims, wherein the silica or silica derivative is at the most partly present in precipitated form.

21. Use according to claim 20, where the silica or silica derivative is not present in precipitated form.

22. Use according to any of the preceding claims, wherein the pharmaceutically acceptable material has an oil absorption value of at least about 100 g oil/100 g such as, e.g., at least about 150 g oil/100 g, at least about 200 g oil/100g, at least about 250 g oil/100 g, at least about 300 g oil/100 g, or at least about 400 g oil/100 g pharmaceutically acceptable material.

23. Use according to any of the preceding claims, wherein the pharmaceutically acceptable material has a BET surface area of at least 5 m^2/g such as, e.g., at least about 25 m^2/g, at least about 50 m^2/g, at least about 100 m^2/g, at least about 150 m^2/g, at least about 200 m^2/g, at least about 250 m^2/g or at least about 275 m^2/g.

24. Use according to any of the preceding claims, wherein the flowability of the silica or silica derivative loaded with 25% w/w or more such as, e.g. 30% w/w or more, 40% w/w or more, 45% w/w or more, 50% w/w or more, 55% w/w or more, 60% w/w or more, 65% w/w or more or about 70% w/w viscoleo meets the Ph. Eur. requirements.

25. Use according to any of the preceding claims, wherein the silica or silica derivative in itself meets the requirements with respect to flowability when tested according to the Threshold Test described herein either with or without any content of viscoleo.

26. Use according to any of the preceding claims, wherein the mean particle size is about 5-50 μm such as e.g. about 30 μm.

27. Use according to any of the preceding claims, wherein the silica or silica derivative is selected from the group consisting of silica acid or a derivative or salt thereof including silicates, silicon dioxide and polymers thereof; silica silylates, silica dimethylsilylates, magnesium aluminosilicate and/or magnesium aluminometasilicate, bentonite, kaolin, magnesium trisilicate, montmorillonite and/or saponite.

28. Use according to any of the preceding claims, wherein the silica or silica derivative comprises silica acid or a derivative or salt thereof.

29. Use according to any of the preceding claims, wherein the silica or silica derivative comprises silicon dioxide or a polymer thereof.

30. Use according to any of the preceding claims, wherein the silica or silica derivative is a silicon dioxide product like Aeroperl® such as, e.g., Aeroperl® 300 or Aeroperl® R 806/30 (silica silylate) (available from Degussa, Frankfurt, Germany).

31. Use according to any of the preceding claims as an oil sorption material for the preparation of pharmaceutical, cosmetic, nutritional and/or food compositions.

32. Use according to any of the preceding claims for the preparation of a solid composition.

33. Use according to any of the preceding claims for sorption of about 5% w/w or more, such as, e.g., about 10% w/w or more, about 15% w/w or more, about 20% w/w or more, about 25% w/w or more, about 30% w/w or more, about 35% w/w or more, about 40% w/w or more, about 45% w/w or more, about 50 w/w or more, about 55% w/w or more, about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more or about 80% w/w or more of an oil or an oily material to obtain a solid material.

34. Use according to any of claims 30-33 for the preparation of pharmaceutical compositions.

35. Use according to any of claims 30-34 for the preparation of particulate materials, granules, pellets, microspheres, nanoparticles.

36. Use according to any of claims 34-35 for the preparation of oral dosage forms.

37. Use according to claim 36, wherein the oral dosage form is in the form of tablets, sachets, capsules.

38. Use according to claim 36 or 37, wherein the oral dosage form is intended for administration via the oral, buccal or sublingual administration route.

39. A solid pharmaceutical particulate material comprising

i) an oil or an oily-like material,

ii) a silica or silica derivative as defined in any of claims 1-38,

wherein the concentration of the oil or oily-like material in the particulate material is about 5% w/w or more such as, e.g., about 10% w/w or more, about 15% w/w or more, about 20% w/w or more, about 25% w/w or more, about 30% w/w or more, about 35% w/w or more, about 40% w/w or more, about 45% w/w or more, about 50 w/w or more, about 55% w/w or more, about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more, about 80% w/w or more, about 85% w/w or more, about 90% w/w or more or about 95% w/w or more .

40. A solid pharmaceutical particulate material according to claim 39, wherein the concentration of the oil or oily-like material is in a range from about 20% to about 80% w/w such as, e.g., from about 25% to about 75% w/w.

41. A solid pharmaceutical particulate material comprising

i) an oil or an oily-like material,

ii) a silica or silica derivative as defined in any of claims 1-38,

wherein the concentration of the silica or silica derivative in the particulate material is about 5% w/w or more such as, e.g., about 10% w/w or more, about 15% w/w or more, about 20% w/w or more, about 25% w/w or more, about 30% w/w or more, about 35% w/w or more, about 40% w/w or more, about 45% w/w or more, about 50 w/w or more, about 55% w/w or more, about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more, about 80% w/w or more, about 85% w/w or more, about 90% w/w or more or about 95% w/w or more .

42. A solid pharmaceutical particulate material according to claim 33, wherein the concentration of the silica or silica derivative is in a range from about 20% to about 80% w/w such as, e.g., from about 20% to about 75% w/w, from abut 20 % to about 50% w/w or from about 20% to about 40% w/w.

43. A solid pharmaceutical particulate material according to claim 39 comprising

i) 25-75% w/w of an oil or an oily-like material, and

ii) 25-75% w/w of a silica or silica derivative as defined in any of claims 1-38,

with the proviso that the total concentration of i) and ii) does not exceed 100% w/w.

44. A solid pharmaceutical particulate material according to any of claims 39-43, wherein the oil or oily-like material is a pharmaceutically inert material.

45. A solid pharmaceutical particulate material according to any of claims 39-43 further comprising a therapeutically, prophylactically and/or diagnostically active substance.

46. A solid pharmaceutical particulate material according to claim 45, wherein the therapeutically, prophylactically and/or diagnostically active substance is solid at ambient temperature.

47. A solid pharmaceutical particulate material according to any of claims 45-46, wherein the therapeutically, prophylactically and/or diagnostically active substance is at least partly including totally present in the form of a solid dispersion including a solid solution.

48. A solid pharmaceutical particulate material according to claim 47, wherein the therapeutically, prophylactically and/or diagnostically active substance is dispersed or dissolved in the oil or oily-like material.

49. A solid pharmaceutical particulate material according to any of claims 39-48 further comprising a pharmaceutically acceptable excipient.

50. A solid pharmaceutical particulate material according to claim 49, wherein the pharmaceutically acceptable excipient is selected from the group consisting of fillers, disintegrants, binders, diluents, lubricants and glidants.

51. A solid pharmaceutical particulate material according to any of claims 39-50 further comprising an pharmaceutically acceptable additive selected from the group consisting of flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, anti-oxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents, absorption enhancing agents

52. A pharmaceutical composition comprising a therapeutically, prophylactically and/or diagnostically active substance and about 5% w/w or more such as, e.g., about 10% w/w or more, about 15% w/w or more, about 20% w/w or more, about 25% w/w or more, about 30% w/w or more, about 35% w/w or more, about 40% w/w or more, about 45% w/w or more, about 50 w/w or more, about 55% w/w or more, about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more, about 80% w/w or more, about 85% w/w or more, about 90% w/w or more or about 95% w/w or more of the silica or silica derivative defined in any of claims 1-38.

53. A pharmaceutical composition according to claim 52 comprising about 5% w/w or more such as, e.g., about 10% w/w or more, about 15% w/w or more, about 20% w/w or more, about 25% w/w or more, about 30% w/w or more, about 35% w/w or more, about 40% w/w or more, about 45% w/w or more, about 50 w/w or more, about 55% w/w or more, about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more, about 80% w/w or more, about 85% w/w or more, about 90% w/w or more or about 95% w/w or more of an oil or an oily-like material,

with the proviso that the total concentration of ingredients does not exceed 100% w/w.

54. A pharmaceutical composition according to claim 52 or 53 in solid form.

55. A pharmaceutical composition according to any of claims 52-54 comprising a solid pharmaceutical particulate material according to any of claims 39-51.

56. A method for the preparation of a pharmaceutical composition comprising about 5% w/w or more such as, e.g., about 10% w/w or more, about 15% w/w or more, about 20% w/w or more, about 25% w/w or more, about 30% w/w or more, about 35% w/w or more, about 40% w/w or more, about 45% w/w or more, about 50 w/w or more, about 55% w/w or more, about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more, about 80% w/w or more, about 85% w/w or more, about 90% w/w or more or about 95% w/w or more of an oil or an oily-like material, the method comprising loading the oil or oily-like material to a silica or silica derivative defined in any of claims 1-38.

57. A method according to claim 56, wherein the composition is in solid form.

58. A method according to claim 55 or 56 wherein the loading is performed by mixing, spraying and/or pouring.

59. A method according to any of claims 56-58, wherein the loading is performed by melt agglomeration or controlled agglomeration.

60. A method according to claim 59, wherein the controlled agglomeration is performed by
i) spraying a first composition in liquid form comprising an oil or an oily-like material on a second composition in solid form comprising a silica or silica derivative as defined in any of claims 1-38, and
ii) mixing or other means of mechanical working the second composition onto which the first composition is sprayed to obtain a pharmaceutical particulate material, which optionally may be further processed to obtain a pharmaceutical dosage form.

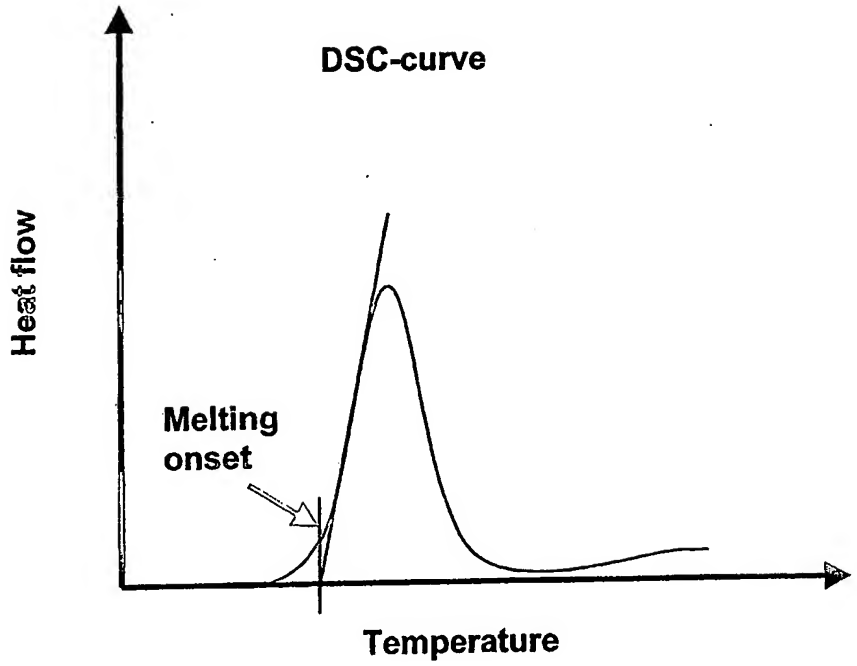

Fig. 1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2004/000112

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/18 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/004001 A (PHAROTECH A/S) 16 January 2003 (2003-01-16) cited in the application page 1, line 29 - page 2, line 29 page 22, line 30 - page 23, line 25 examples 7,8 claims	1-60
X	EP 1 241 134 A (DEGUSSA AG) 18 September 2002 (2002-09-18) page 2, line 3 - line 34 page 12 - page 13 claims 1-3	1-60

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 June 2004	22/06/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Epskamp, S

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2004/000112

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 163 178 A (BEECHAM GROUP PLC) 4 December 1985 (1985-12-04) page 1, paragraph 4 - page 2, paragraph 4 page 3, paragraph 2 - page 4, paragraph 1 examples claims	1-60
X	US 3 400 197 A (LIPPMANN) 3 September 1968 (1968-09-03) column 2, line 52 - line 58 column 3, line 46 - column 4, line 5 examples claims	1-60
X	US 4 603 143 A (SCHMIDT) 29 July 1986 (1986-07-29) column 1, line 38 - line 49 example 1 claims	1-60
X	EP 0 345 109 A (RHONE-POULENC CHIMIE) 6 December 1989 (1989-12-06) page 1, line 1 - line 26 examples claims	1-60
X	FR 2 767 071 A (RHODIA CHIMIE) 12 February 1999 (1999-02-12) page 1, line 5 - line 7 page 1, line 22 - line 29 examples claims	1-60
X	EP 1 004 296 A (EISAI CO LTD ; FUJI CHEM IND CO LTD (JP)) 31 May 2000 (2000-05-31) paragraph '0004! - paragraph '0005! paragraph '0009! paragraph '0018! - paragraph '0020! examples claims	1-60

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK2004/000112

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 03004001 A	16-01-2003	CA	2452330 A1	16-01-2003
		WO	03004001 A1	16-01-2003
		EP	1406594 A1	14-04-2004
EP 1241134 A	18-09-2002	DE	10112651 A1	19-09-2002
		CA	2376843 A1	16-09-2002
		CN	1375453 A	23-10-2002
		EP	1241134 A2	18-09-2002
		JP	2002326809 A	12-11-2002
		US	2003059380 A1	27-03-2003
EP 0163178 A	04-12-1985	AU	589561 B2	19-10-1989
		AU	4280085 A	28-11-1985
		CA	1255222 A1	06-06-1989
		DE	3580304 D1	06-12-1990
		EP	0163178 A2	04-12-1985
		ES	8800039 A1	01-01-1988
		GR	851254 A1	25-11-1985
		IE	57732 B1	24-03-1993
		JP	2096181 C	02-10-1996
		JP	7072128 B	02-08-1995
		JP	60258113 A	20-12-1985
		MX	163564 B	01-06-1992
		NZ	212148 A	06-01-1989
		US	4859709 A	22-08-1989
		US	4719228 A	12-01-1988
		ZA	8503823 A	30-04-1986
US 3400197 A	03-09-1968	AT	267068 B	10-12-1968
		BE	675379 A	31-05-1966
		DK	115350 B	29-09-1969
		FR	5137 M	05-06-1967
		FR	1465919 A	13-01-1967
		GB	1113860 A	15-05-1968
		IL	24813 A	25-06-1969
		NL	6516147 A	27-07-1966
		NO	119439 B	19-05-1970
US 4603143 A	29-07-1986	CA	1210697 A1	02-09-1986
EP 0345109 A	06-12-1989	FR	2631620 A1	24-11-1989
		AT	94511 T	15-10-1993
		AU	3496789 A	23-11-1989
		BR	8902688 A	23-01-1990
		CN	1042132 A ,B	16-05-1990
		CN	1086740 A ,B	18-05-1994
		DE	68909113 D1	21-10-1993
		DE	68909113 T2	17-03-1994
		DK	240589 A	20-11-1989
		EP	0345109 A1	06-12-1989
		ES	2058568 T3	01-11-1994
		FI	892410 A	20-11-1989
		HU	50724 A2	28-03-1990
		JP	1801239 C	12-11-1993
		JP	2044023 A	14-02-1990
		JP	5005768 B	25-01-1993
		KR	9409929 B1	19-10-1994
		NO	891989 A	20-11-1989

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK2004/000112

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0345109 A		NZ 229162 A	26-02-1991
		SU 1836290 A3	23-08-1993
		TR 23943 A	21-12-1990
		US 5635214 A	03-06-1997
		YU 101589 A1	28-02-1991
		ZA 8903716 A	24-04-1991
FR 2767071 A	12-02-1999	FR 2767071 A1	12-02-1999
		AU 8988398 A	01-03-1999
		CA 2267093 A1	18-02-1999
		CN 1237091 T	01-12-1999
		EP 0966207 A1	29-12-1999
		WO 9907237 A1	18-02-1999
		JP 3411585 B2	03-06-2003
		JP 2000507834 T	27-06-2000
		RU 2201100 C2	27-03-2003
		TR 9901201 T1	22-11-1999
		TW 492846 B	01-07-2002
		US 2003215485 A1	20-11-2003
		US 2001051176 A1	13-12-2001
EP 1004296 A	31-05-2000	JP 2000044462 A	15-02-2000
		EP 1004296 A1	31-05-2000
		WO 9961000 A1	02-12-1999
		US 2002142043 A1	03-10-2002